REMARKS

Reconsideration and withdrawal of the rejections are respectfully requested in view of the amendments are remarks presented herein.

Status of the Claims

By this Amendment, claims 1, 2, 4, 8, and 9, have been amended and claims 10-12 have been added, as discussed further below. Support can be found throughout the specification and claims as originally filed. For example, for new claims 10-12 support includes compound 4(a), page 5, line 20 – page 6, line 1, and page 8, lines 14-18. No new matter has been added.

Claims 1-12 are currently pending.

Rejections Under 35 U.S.C. § 112

Claims 1-9 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The following specific issues have been raised.

(i) The Examiner contends that claim 1 does not meet the requirements of second 112, second paragraph, because some of the chemical structures are partially hand drawn and illegible. (Office Action, pg. 2.) As suggested by the Examiner, without narrowing the scope of the claims in any way, the chemical structures have been re-drawn in order to moot the rejection.

(ii) The Examiner also contends that claim 1 presents uncertainty with respect to the acylation and is not grammatically correct. (Office Action, pg. 2.) As suggested by the Examiner to moot the rejection, without narrowing the scope of the claims in any way, claim 1 has been amended to reorganize the formula to appear after each recitation, and to correct the final period.

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(iii) The Examiner contends that "[t]he identity of the acyl donor, required in the process of claim 1, is undefined," and has limited the interpretation to those specifically exemplified in the specification. (Office Action, pg. 3) However, "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow. This means that the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the specification." MPEP § 2111.02 (citations omitted). While the specification may be consulted for definitions, "extraneous limitations cannot be read into the claims from the specification or prosecution history." *Bayer AG v. Biovail Corp.*, 61 USPQ2d 1675, 1681 (Fed. Cir. 2002) (citations omitted). Thus, in the absence of any confusion on the art recognized meaning of "acyl donor," it is improper to limit that scope of the claims to those exemplary acyl donors identified in the specification. Accordingly, to the extent that the claims have been rejected based on the use of the term "acyl donor," Applicants respectfully traverse the rejection and request that the full scope of the claims be examined without reading in limitations from the specification.

(iv) The Examiner rejected claim 1 for the definitions of substituents on R^1, R^2, and R^3, and allegedly inconsistencies in the types of heteroatoms. (Office Action, pg. 3.) Without narrowing the scope of the claims in any way, the clause in question has been removed by the present amendment, and new claim 10 has been added. Accordingly, the rejection is moot. Reconsideration and reexamination of the full scope of the claim are respectfully requested.

(v) The Examiner rejected claim 1 for improper grammar with respect to cyclization of two groups selected from R^1, R^2, and R^3. (Office Action, pg. 4.) The claim has been

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amended to recited that "R^1 and R^2 can be cyclized each with other," as more specifically shown in the listing herein. Accordingly, the rejection is moot.

(vi) Claim 2 was rejected for issues of antecedent basis. (Office Action, pg. 4.) The rejection is moot in view of the amendments to claim 1 presented herein.

(vii) Claim 4 was rejected for the clause "the most preferably Cl." (Office Action, pg 4.) Without narrowing the scope of the claims in any way, this clause has been eliminated to moot the rejection.

(viii) Claim 9 was rejected for antecedent basis issues related to "said arly ester" and for use of the term "alkenyl acetate." (Office Action, pg. 5.) This rejection is moot in view of the amendments presented herein. Claims 11 and 12, related to original claim 9, have also been added. The issue related to the scope of the acyl donor is respectfully traversed, for the reasons set forth in paragraph (iii), above.

(ix) The rejections of claims 3 and 5-8 as dependent on allegedly indefinite base claims are believed to be moot.

Reconsideration and withdrawal of the rejections under section 112, second paragraph, are respectfully requested.

Specification

The specification was rejected for having an Abstract of more than 25 lines or 250 words. (Office Action, pg. 9.) This rejection is moot in view of the substitute Abstract presented herewith.

The specification was rejected for containing spelling errors. (Office Action, pg. 9.) The rejection is moot in view of the amendment to the specification presented herewith.

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Reconsideration and withdrawal of the rejections are respectfully requested.

Rejecti ns Under 35 U.S.C. § 103

Claims 1-9 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Persson et al., *J. Am. Chem. Soc.* vol. 121, pp. 1645-1650 (February 13, 1999) ("Persson") in view of Koh et al., *Tetrahedron Letters*, vol. 39, pp. 5545-5548 (1998) ("Koh"), and in further view of Mahmoudian et al., *Biotechnol. Appl. Biochem.* vol. 29, pp. 229-233 (1999) ("Mahmoudian"). Applicants respectfully disagree with and traverse the rejection.

The Examiner's argument and characterizations of the references are summarized below, and the deficiencies of the rejection are then addressed.

A. The Examiner's proposed combination.

1. Persson

The Examiner contends that Persson discloses a dynamic kinetic resolution (DKR) process where a racemic alcohol according to Applicants' claimed formula (4) is converted to an enantiopure chiral alcohol in the presence of a ruthenium complex and *C. Antarctica* lipase. (Office Action, pg. 6, ln. 10-12.) The Examiner recognizes that Persson does not disclose a DKR process employing a ruthenium complex within the scope of the presently claimed invention. (Office Action, pg. 6, ln. 23 – pg. 7, ln. 2.) The Examiner further recognizes that Persson states that a triphenylphospine-liganded ruthenium complex (Persson compound 1, pg 1646) is not feasible for use in DKR in combination with lipase due to the requirement for inorganic hydroxide that would interfere with the enzyme. (Office Action, pg. 6, ln. 13-19.) Specifically, Persson states

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that the triphenylphosphine Ru complex "requires the presence of NaOH, which may interfere with the enzymes" used in DKR. (Persson, pg. 1646.)

2. Koh

The Examiner contends that Koh discloses a racemization process using a base (potassium hydroxide, potassium *t*-butoxide, potassium carbonate, sodium hydride, or triethylamine ("TEA")) together with a ruthenium complex according to Applicants' claimed formula (1). (Office Action, pg. 7, ln. 9-11.) The Examiner also contends that Koh "expressly suggests incorporating this ruthenium complex into a" DKR process. (Office Action, pg. 6, ln. 7-8.) The Examiner further contends that Koh teaches away from the use of an alkoxide as the base in a DKR where the ruthenium complex is coupled with lipase, because the alkoxides react with the acyl donors necessary DKR. (Office Action, pg. 7, ln. 12-15.) In this regard, Koh states that "attempts to combine lipase-catalyzed acylation with our catalytic racemization system were not fruitful due to predominant chemical acylation of alkoxides." (Koh, pg. 5548.)

3. Mahmoudian

The Examiner contends that Mahmoudian "teaches that the addition of triethylamine [(TEA)] to the reaction mixture wherein *C. Antarctica* lipase is employed in the acetylation of the drug '506U78' increased reaction rates and decreased the formation of side produce." (Office Action, pg. 8, ln. 10-14). More particularly, what Mahmoudian states is that the "[a]ddition of TEA (10% v/v) to reaction mixtures also improved rates, but this resulted in increased levels (up to 20%) of other related impurities .... Lowering the concentration of TEA to 1% (v/v) did not, however,

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signiicantly (sic) affect either bioconversion rates or impurity profile ...." (Mahmoudian, pg. 231.)

4. The proposed combination of Persson in view of Koh and Mahmoudian.

The Examiner apparently recognizes that, in view of disclosures in both Koh and Persson alone, there would have been no motivation to use a Ru complex according to Koh in a DKR process according to Persson. This is at least because the required hydroxide "may interfere with the enzymes" (Persson, pg. 1646), and because of the undesirable "predominate chemical acylation of alkoxides" (Koh, pg. 5548). Instead, the Examiner contends that there would have been motivation to use Koh's Ru complex in Persson's DRK process with TEA as a base. In essence, the Examiner is relying on:

- Persson for the general DRK process in the presence of a ruthernium complex and *C. Antarctica* lipase;
- Koh for
    - disclosing a Ru complex within the scope of claimed formula (1),
    - suggesting use of the Ru complex in a DKR process, and
    - suggesting the use of TEA as a base with the Ru complex; and
- Mahmoudian for the use of TEA in combination with *C. Antarctica* lipase.

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More specifically, the Examiner contends that:

> [o]ne of ordinary skill, motivated by the desire to avail himself of the superior racemization activity of the complex studies in the Koh et al reference, would have to select either sodium hydride, potassium carbonate or triethylamine as the base he would employ in the ruthenium complex—lipase system. ... that triethylamine is the appropriate base to select from this group is at once obvious. ... [Koh] does not teach that these less-effective bases [e.g., triethylamine] are totally inactive.

(Office Action, pg. 7, ln 16- pg. 8, ln. 9.) In view of the characterization of Mahmoudian as disclosing that TEA with *C. Antarctica* lipase increases reaction rates and decreased the formation of side produce in the acetylation of the drug '506U78', the Examiner contends that one would have selected TEA as the basic reagent employed in combination with the ruthernium complexes of Koh formula 1a in a DRK with *C. Antarctica* lipase "despite Koh et al's observation that [TEA] is much less effective than potassium hydroxide" (Office Action, pg. 8, ln. 18-19)

B. There would have been no motivation for the proposed modification—Triethylamine is inactive and causes unwanted by-products.

Contrary to the contentions in the Office Action (Office Action, pg. 7, ln 16- pg. 8, ln. 9), the selection of TEA for use with Koh's Ru complex in Persson's DKR process would not have been obvious. According to Koh, (1) the Ru catalyst is totally inactive with TEA, and according to Mahmoudian (2) TEA causes unwanted by-products with enzymes. In view of these problems, discussed further below, there would have been no motivation to select TEA, as proposed.

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1. Ru catalysis is totally inactive in the pr sence of TEA

The Examiner contends that Koh "does not teach that these less-effective bases [e.g., triethylamine] are totally inactive." (Office Action, pg. 8, In. 6-9.) This statement is correct to the extent that not all the organic bases in Koh are totally inactive, and to the extent that Koh does not say in words that all the organic bases are totally inactive. Applicants also agree that the relevant text of Koh only states that "the organic bases such as ... triethylamine are less effective than potassium hydroxide." (Koh, pg. 5546, In. 5-6.)

However, any characterization of Koh as teaching racemization activity with TEA as the base is simply incorrect. Koh expressly teaches that Ru catalyzed racemization using triethyamine is completely inactive. The statement "[TEA] is much less effective than potassium hydroxide" (Office Action, pg. 8, In. 18-19), is a gross understatement to the extent it implies that TEA is in anyway effective in Koh.

More specifically, Koh demonstrates that when their ruthenium complex is used with KOH, complete (or nearly complete) racemization occurs in 20 minutes.

Entry No.	Ru complex	Base	Time	%ee[1]
2	1a	KOH	20 min	0
3	1b	KOH	20 min	8
4	1c	KOH	20 min	28

(Koh, Table 1, pg. 5546.) In contrast to the complete or nearly complete (0-28%ee) racemization using Ru complex 1a with KOH in 20 minutes, Koh demonstrates a complete absence of any conversion using Ru complex 1a with TEA over 24 hours.

[1] Note that a lower %ee indicates superior activity, as evidenced by, for example, the 99%ee for Koh entry no. 1, where no Ru catalyst was present and no conversion took place.

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Entry No.	Ru complex	Base	Time	%ee
16	1a	Et_3N	24 hrs	99

(Koh, Table 1, pg. 5546). In fact, TEA is the worst possible base to use according to Koh, since all the other bases yield at least some racemization. (Koh, Table 1, pg. 5546, entries 12 (BuOK), 13 (NaH), 14 (K_2CO_3), and 15 (DBU).) Koh's data showing a complete absence of an Ru catalyzed conversion in the presence of triethylamine is an express teaching that Ru catalyzed racemization using triethyamine is completely inactive.

Thus, if, as argued by the Examiner "[o]ne of ordinary skill, motivated by the desire to avail himself of the superior racemization activity of the complex studies in the Koh et al. reference, would have to select either sodium hydride, potassium carbonate or triethylamine [(TEA)] as the base he would employ in the ruthenium complex—lipase system," the last choice of base would be TEA, which provided no racemerization even after 24 hours. Accordingly, in view of the absence of any conversion using triethylamine and the fact that all the other organic bases were superior, there would have been no motivation to select TEA for use with in a ruthenium complex—lipase system of any type, including the DKR process of Persson.

2. TEA causes unwanted by-products with enzymatic reactions.

The Examiner contends that Mahmoudian would have provided motivation for using TEA with an enzyme because TEA "increased reaction rates and decreased the formation of side products." (Office Action, pg. 8, ln 10-14.) However, according to Mahmoudian, "[a]ddition of TEA ... improved rates, but this resulted in increased levels (up to 20%) of other related impurities ...." (Mahmoudian, pg. 231; Tables 2 and 3.)

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Thus, Mahmoudian does not teach TEA "decreased the formation of side produce" (Office Action, pg. 8, ln. 10-14), but just the opposite. If Mahmoudian provides any motivation, it is motivation to not use the impurity causing TEA.

Further, the final reaction conditions of Mahmoudian make no mention of using the impurity causing TEA. (See Mahmoudian, pg. 233.) This implies that, after systematically evaluating its effects, Mahmoudian rejected the use of TEA in their enzymatic reaction. Mahmoudian did not prefer TEA in an enzymatic reaction and did not recommend its use, and one skilled in the art reading Mahmoudian would not have been motivated to use TEA in an enzymatic reaction.

C. Reliance on Mahmoudian is misplaced, and Mahmoudian does not provide the required motivation.

Technically, the Examiner's reliance on Mahmoudian for disclosing the addition of TEA to a reaction mixture wherein *C. Antarctica* lipase is employed in the acetylation of drug "506U78," is of no relevance to the Ru catalyzed racemizations of Persson and Koh. As acknowledged by the Examiner, both Persson and Koh show that Ru catalysis is particularly complex, and that it raises unique issues and concerns. Thus, there is no basis for extrapolating the alleged effectiveness of TEA in Mahmoudian to the vastly different conditions in Persson and Koh. Hence, one skilled in the art would not have relied upon Mahmoudian as a teaching or suggestion for modifying Persson and Koh, as proposed in the present rejection.

Legally, as explained below, Mahmoudian is non-analogous art, and thus cannot be relied upon for the present rejection under 35 U.S.C. §103.

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1. Non-analogous art cannot be used to support a rejection under 35 U.S.C. §103.

A prior art reference must be "analogous prior art" for the purpose of analyzing the obviousness of the present invention. M.P.E.P. § 2141.01(a). In order for a reference to be analogous art, the reference must either (1) be in the current invention's field of endeavor, or (2) be reasonably pertinent to the particular problem with which the inventors were concerned. See *In re Oetiker*, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). If the reference is non-analogous art, it cannot be used to support a rejection under 35 U.S.C. §103. M.P.E.P. § 2141.01(a). That is, "[t]he combination of elements from non-analogous sources, in a manner that reconstructs the applicant's invention only with the benefit of hindsight, is insufficient to present a *prima facie* case of obviousness." *Oetiker*, at 1446. In the present case, Mahmoudian is not part of an art analogous to the presently claimed process for preparing a chiral ester comprising reaction using a ruthenium complex.

2. Mahmoudian is non-analogous art to the present invention.

The field of invention of the present invention a process for preparing an optically pure chiral ester from a racemic alcohol by dynamic kinetic resolution ...." (Specification, page 1, lines 1-3.) The problem and need identified in the present application is to overcome the problem that although DRK can yield high optical purity, 12 to 40% of a ketone by-product is produced. (Specification, pg. 1, ln. 9-18.)

In contrast, Mahmoudian is non-analogous art directed to a reaction process unrelated to any issues of chirality. Mahmoudian involves the acylation of an anti-leukamia agent. More specifically, Mahmoudian's goal and the problems it addresses

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are the "regioselective acylation of 506U78 at the 5'-position; .... [in order] to render the compound more soluble and bioavailable," and the optimization of this reaction. (Mahmoudian, pg. 229.)

Cleary, Mahmoudian is direct to a different field of endeavor and different problem than the present invention. The fact that Mahmoudian uses an enzyme does not make within the field of endeavor of the presently claimed invention anymore than the common features of splicing films or tapes for information storage (*King Instrument Corp. v. Otari Corp.*, 226 U.S.P.Q. 402 (Fed. Cir. 1985)) or foams for uses related to petroleum (*In re Clay,* 23 U.S.P.Q.2d 1058 (Fed. Cir. 1992)) define common fields of endeavor. As in *King*, a field of endeavor is narrowly defined and is based on the object or direction of the invention. Just as the field of endeavor of the invention and reference in *Clay* was not "maximizing withdrawal of petroleum stored in petroleum reserves," the field of endeavor of present invention and Mahmoudian is not "enzymatic reactions" Further, just as all fastening devices (*In re Oetiker*, 24 U.S.P.Q2d 1443, 1446 (Fed. Cir. 1992)) and all computer memory modules (*Wang Laboratories Inc. v. Toshiba Corp.*, 26 U.S.P.Q. 1767, 1773 (Fed. Cir. 1993)) do not involve the same problem, all enzymatic reactions do not involve the same problem to be solved.

Rather than being analogous art, the field of endeavor and problem to be solved of the present invention relate to forming optically pure chiral ester while Mamoudian relates to an enzymatic acylation of an anti-leukemia drug. Consequently, since the

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fields of endeavor and problems to be solved are not the same, Mahmoudian is non-analogous art,[2] and cannot be relied upon for a rejection under section 103.

D. Conclusion with respect to section 103 rejection.

Persson and Koh teach away from using certain ruthenium complexes in a DKR process. The Examiner's contention that one would have been motivated to use the Ru complex in DKR with TEA as a base is unsupported, since Koh shows that Ru catalysis is inactive with TEA and Mahmoudian shows that TEA causes unwanted by-products in enzymatic reactions. Any reliance on Mahmoudian is also legally erroneous because the reference is non-analogous art to the present invention.

Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

The Examiner is invited to contact Applicants' undersigned representative by telephone at (202) 408-4092 to address any issues that may remain.

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[2] Additionally, Mahmoudian is directed to a field of endeavor and problems distinct from those of both Persson and Koh.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: November 21, 2003

By: _____
Mark J. Feldstein
Reg. No. 46,693

Attachment: **Substitute Abstract**

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